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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/838,968	04/20/2001	Michael B. Foster	RENAS/03	1662

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 12/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/838,968	FOSTER, MICHAEL B.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-11 and 13-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-11 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The finality of the previous Office Action dated May 19, 2003 is withdrawn due to a new ground of rejection.

Status of the Claims

2. Claims 1-3, 5-11 and 13-16 are pending.

Applicants' Supplemental After Final Amendment filed on November 18, 2003, and Applicants' Appeal Brief filed March 17, 2004 are acknowledged. Applicants' response has been fully considered. In the Supplemental Amendment, claim 10 has been amended. Thus, claims 1-3, 5-11 and 13-16 are examined.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

3. The previous rejection of claims 2, 3, 10, 11, 13, 15 and 16 under 35 U.S.C. 112 second paragraph, is withdrawn in view of applicants' amendment to the claim in the supplemental amendment filed November 18, 2003, and applicants' argument at pages 6-8 and Appendices B and C in the Appeal Brief filed March 17, 2004.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1, 7-10 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Drake *et al.* (J. Clinical Endocrinology 47, 571-581 (1997)).

Drake *et al.* teaches a method for optimizing growth hormone replacement therapy in hypopituitary adult; the method comprising determining the levels of insulin-like growth factor-1 (IGF-1; claims 7 and 13) or IGF binding protein 3 (IGFBP-3) in response to an initial dose (0.8 or 0.4 IU daily) of hGH (Genotropin, claims 1, step 1), increasing the dose of hGH until serum level of IGF-1 between the median and the upper end of the age-related reference range is achieved (claim 1 (steps 2 & 3); abstract, page 3914, left column, second paragraph), establishing the dosage of hGH needed to maintain target IGF-1 levels, and administering the established dose of hGH (Claims 1 (step 4) and 10; page 3914; Fig. 1). The initial dose of 0.8 or 0.4 IU daily (1 IU = 330 μg) corresponds to 5.5 or 2.8 μg/day/kg for female (assuming 48 kg), which is about 4 μg/day/kg (claim 9), or, 3.8 or 1.9 μg/day/kg for male (assuming 70 kg), which is about 2 μg/day/kg (claim 8).

4. Claims 1, 5-10, 13 and 14 are rejected under 35 U.S.C. 102(a) as being anticipated by Murray *et al.* (Clinical Endocrinology 52, 537-542 (May 2000)).

Murray *et al.* teaches using an individualized low-dose titration regimen for a growth hormone replacement therapy in adult with GH deficiency; the method comprising determining the levels of insulin-like growth factor-1 (IGF-1; claims 7 and 13) in response to an initial dose (0.8 IU daily) of hGH (Genotropin, claims 1 & 14 (step 1)), adjusting the dose of hGH by 0.2 or 0.4 IU/day increments until serum level of IGF-1 reaches in the range of the age-related mean for the normal population (claims 1 & 14 (steps 2 & 3); page 538), establishing the dosage of hGH needed to maintain target IGF-1 levels, and administering the established dose of hGH (claims 1

(step 4) and 10; page 539; Table 1). The initial dose of 0.8 IU daily (1 IU = 330 μg) corresponds to 5.5 μg/day/kg for female (assuming 48 kg), which is about 4 μg/day/kg (claim 9), or, 3.8 μg/day/kg for male (assuming 70 kg), which is about 2 μg/day/kg (claim 8). The median value of the maintenance dose for female is 1.6 IU/day (range 0.4-2.4), which corresponds to 11 μg/day/kg (range 2.8-17; page 539; claims 6 and 14 (step 4)). The median value of the maintenance dose for male is 0.8 IU/day (range 0.4-2.0), which corresponds to 3.8 μg/day/kg (range 1.9-9.4), the maintenance dose of 9.4 μg/day/kg is about 10 μg/day/kg (claim 5) absent definition in the specification.

Response to Brief On Appeal

In the Brief On Appeal, Section (5) states summary of the invention, the inventive method replenishes human growth hormone (hGH) in an adult by administering an initial hGH dose, then determining the individual's response to the initial dose, determining the optimal dose for that individual, and then administering that optimal dose as a maintenance dose to replenish hGH, and human growth hormone is the only active agent administered, there are no other hormones or other active agents in the composition (page 3, line: 19-21); Sections (6) and (7) states the issues and groups of claims, Issue (I): Whether claims 2, 3, 11, 15 and 16 are indefinite under 35 U.S.C. 112, second paragraph; Issue (II): Whether claims 1, 7-10 and 13 are anticipated by Drake et al. (1998); and Issue (III). Whether claims 1, 5-10, 13 and 14 are anticipated by Murray et al. (2000); Section (8) states appellants' arguments; Section (9) states Summary; Section (10) Appendix.

Applicants' response in Brief On Appeal has been fully considered, the arguments on the rejection of claims 2, 3, 11, 15 and 16 being indefinite under 35 U.S.C. 112, second paragraph are persuasive, thus the rejection is withdrawn.

Regarding the rejection of claims 1, 7-10, and 13 being anticipated under 35 U.S.C. 102(b) over Drake and the rejection of claims 1, 5-10, 13 and 14 being anticipated under 35 U.S.C. 102(a) over Murray, applicants indicate that a reference must disclose each and every limitation of the claims in order to anticipate, neither Drake or Murray disclose applicant's administration of an individualized dose, and thus do not anticipate applicant's claimed method; as explained in the Foster Declaration, there is considerable variation in setting the target IGF-I level to determine the optimal range of hGH, the inventive method determines an individualized optimal dose. Neither Drake nor Murray disclose applicant's method for individualizing the optimal hGH replenishing dose selecting a dose producing an optimal replenishment; Drake discloses a uniform titration regimen based on a defined target range of serum IGF-1, while the claimed invention determines an optimal dose from an individualized dosing; Drake does not disclose determining a response to a serially increased dose that is predicated on the initial dose, and in Drake's method, there is always the same increase, so that there is no variation in the magnitude, while applicant claims an individualized dose, where a response to an initial dose is determined, then a response to a serially increase dose is determined, then the dose that produces optimal replenishment is selected from the serially increased dose and administered as a maintenance dose; and Murray itself states that "the ideal dosing regimen and determinants of the maintenance dose have, however, yet to be elucidated" (page 537, Summary section). Thus, Murray does not disclose applicant's claimed "optimal response" or "optimal replenishment". The

Examiner's rejection, however, contradicts the reference in finding that Murray has determined the ideal dosing regimen and determinants of the maintenance dose, simply by correlating it with IGF-I levels.

The response has been fully considered, however, the argument is not persuasive because of the following reasons: The claim recites using an individualized maintenance dose to replenish hGH, where the maintenance dose is determined by a response of the human to serially increased doses of hGH and the response is the increased level of IGF-1, and the specification indicates this individualized maintenance dose is determined by attainment of the desired level of IGF-1 (page 6, line 8), however, the specification does not indicate what is the desired value of IGF-1 for an individual and how the desired value is obtained. Furthermore, the specification indicates these maintenance doses, which produce the desired level of hGH replenishment for the individuals, are typically about 10-14 μg/kg/day for males and about 14-20 μg/kg/day for females, and the levels of IGF-1 serves as mediator of anabolic effects of hGH therapy (page 6, lines 4-15); and all three Examples of hGH therapy (pages 7-12 of the specification) indicate the IGF-1 of each individual is stable about 300 ng/ml on a daily dose of 600 or 800 μg/day in the treatment. Thus, as indicated in the specification, it appears the individualized maintenance dose is determined by a target range of the desired levels of IGF-1 in the claimed method, which is not different from Drake's method using a targeting IGF-1 level of the same age to determine the maintenance dosage. Moreover, Drake discloses after the treatment of initial dose and review of the IGF-1 response, the dose of hGH increased until serum level of IGF-1 between the median and the upper end of the age-related reference range is achieved (abstract, page 3914, left

column, second paragraph), thus the reference discloses all the limitation cited in the claim. Therefore, the claimed invention is anticipated by Drake *et al.*

Regarding Murray's statement that "the ideal dosing regimen and determinants of maintenance dose have, yet to be elucidated", which is the objective Murray intends to achieve, and Murray has shown GH dose required in an individual is dependent on the serum IGF-1 levels, and an individualized low-dose titration regimen aimed at normalization of the serum IGF-1 is used for GH therapy. Therefore, the claimed invention is anticipated by Murray *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-3, 5-11 and 13-16 are rejected are rejected under 35 U.S.C. 103(a) as being unpatentable over Murray *et al.* (Clinical Endocrinology 52, 537-542 (May 2000)) taken with Scott *et al.* (U. S. Patent 6,458,387, filed October 18, 1999) and Goodman and Gilman's The Pharmacological Basis of Therapeutics (Pergamon Press, New York 1990, pp. 5-6, 10-13 and 20-32).

Murray *et al.* teach using an individualized low-dose titration regimen for a growth hormone replacement therapy in adult with GH deficiency; the method comprising determining the levels of insulin-like growth factor-1 (IGF-1; claims 7 and 13) in response to an initial dose (0.8 IU daily) of hGH (Genotropin, claims 1 & 14 (step 1)), adjusting the dose of hGH by 0.2 or 0.4 IU/day increments until serum level of IGF-1 reaches in the range of the age-related mean for

the normal population (claims 1 & 14 (steps 2 & 3); page 538), establishing the dosage of hGH needed to maintain target IGF-1 levels, and administering the established dose of hGH (claims 1 (step 4) and 10; page 539; Table 1). The initial dose of 0.8 IU daily (1 IU = 330 μg) corresponds to 5.5 μg/day/kg for female (assuming 48 kg), which is about 4 μg/day/kg (claim 9), or, 3.8 μg/day/kg for male (assuming 70 kg), which is about 2 μg/day/kg (claim 8). The median value of the maintenance dose for female is 1.6 IU/day (range 0.4-2.4), which corresponds to 11 μg/day/kg (range 2.8-17; page 539; claims 6 and 14 (step 4)). The median value of the maintenance dose for male is 0.8 IU/day (range 0.4-2.0), which corresponds to 3.8 μg/day/kg (range 1.9-9.4), the maintenance dose of 9.4 μg/day/kg the upper limit) is about 10 μg/day/kg (claim 5) absent definition in the specification. However, Murray *et al.* do not disclose the maintenance dose is adjusted from a daily dose to a monthly dose based on individualized bioavailability data and administered monthly. Goodman and Gilman teach bioavailability data indicate the extent to which a drug reaches its site of action, or a biological fluid from which the drug has access to its site of action (page 5), and the individualizing dosage can be adjusted based on the pharmacodynamic and pharmacokinetic parameters (pages 21-28), and variations of these parameters in a particular patient (page 30, right column); and Scott *et al.* teach a sustained release microsphere containing a therapeutic protein such as hGH can be produced and administered in therapeutically amounts to subjects daily or monthly, where a therapeutically amount (e.g., 0.01 mg/kg to 1000 mg/kg) will vary with subject's age, condition and the nature of the disease, and can be determined by one of ordinary skill in the art (Table 1; column 3, line 51-column 4, line 4; column 27, lines 1-17). At the time of invention was made, it would be obvious that one of ordinary skill in the art is motivated to use the method taught by Murray *et*

al. to replenish hGH in an individual by adjusting a daily maintenance dosage to a monthly maintenance dosage using a sustained release microsphere containing hGH as taught by Goodman and Gilman, and Scott *et al.* (claims 2, 3, 11, 15 and 16) because the microsphere with the monthly maintenance dosage based on the adjustment of daily maintenance dosage would permit the sustained release of the active agents in a predictable, consistent manner (column 3, lines 10-13). Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Conclusion

6. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Patent Examiner

CMK
November 18, 2004

JON WEBER
SUPERVISORY PATENT EXAMINER